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Short-term memory binding deficits in Alzheimer's disease

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Summary Alzheimer's disease impairs long term memories for related events (e.g. faces with names) more than for single events (e.g. list of faces or names). Whether or not this associative or 'binding' deficit is also found in short-term memory has not yet been explored. In two experiments we investigated binding deficits in verbal short-term memory in Alzheimer's disease. Experiment 1 : 23 patients with Alzheimer's disease and 23 age and education matched healthy elderly were recruited. Participants studied visual arrays of objects (six for healthy elderly and four for Alzheimer's disease patients), colours (six for healthy elderly and four for Alzheimer's disease patients), unbound objects and colours (three for healthy elderly and two for Alzheimer's disease patients in each of the two categories), or objects bound with colours (three for healthy elderly and two for Alzheimer's disease patients). They were then asked to recall the items verbally. The memory of patients with Alzheimer's disease for objects bound with colours was significantly worse than for single or unbound features whereas healthy elderly's memory for bound and unbound features did not differ. Experiment 2 : 21 Alzheimer's disease patients and 20 matched healthy elderly were recruited. Memory load was increased for the healthy elderly group to eight items in the conditions assessing memory for single or unbound features and to four items in the condition assessing memory for the binding of these features. For Alzheimer's disease patients the task remained the same. This manipulation permitted the performance to be equated across groups in the conditions assessing memory for single or unbound features. The impairment in Alzheimer's disease patients in recalling bound objects reported in Experiment 1 was replicated. The binding cost was greater than that observed in the healthy elderly group, who did not differ in their performance for bound and unbound features. Alzheimer's disease grossly impairs the mechanisms responsible for holding integrated objects in verbal short-term memory.

Keywords: Memory binding, Alzheimer's disease, verbal short-term memory

Introduction

In cognition, binding is referred to as the mechanism responsible for representing different pieces of information such as names and faces, colours and shapes into unified objects (Treisman and Gelade, 1980; Zimmer *et al.*, 2006). As an integrative process, binding operates at many cognitive levels, ranging from grouping in perception to storing highly elaborated complex events in memory (i.e. episodes encompassing objects, locations, emotions, dates) (Treisman and Gelade, 1980; Tulving, 2002; Murre *et al.*, 2006). Alzheimer's disease is characterized by progressive neuronal loss. As a consequence, the efficiency of this binding process may decrease dramatically. This paper focuses on memory binding in

Alzheimer's disease. However, since the processes for temporary binding might differ substantially from those requiring the learning of bindings (Logie *et al.*, 2009), we focus here on the process of binding and retaining those bindings in short-term memory.

Associative Learning tasks, and particularly Paired Associates Learning tasks, have been proposed as useful neuropsychological tools for detecting memory changes in the early stages of Alzheimer's disease (Swainson *et al.*, 2001; Fowler *et al.*, 2002; Blackwell *et al.*, 2004; O'Connell *et al.*, 2004). Swainson *et al.* (2001) demonstrated that the Paired Associates Learning task of the Cambridge Neuropsychological Test Automated Battery (CANTAB) was better at differentiating between patients with Alzheimer's disease, from those with depression, Mild Cognitive Impairment, and the healthy elderly, than a battery of other non-associative memory tasks. Fowler *et al.* (2002) assessed a group of Mild Cognitive Impairment patients with the same task and followed them longitudinally. The authors found that those Mild Cognitive Impairment patients whose initial performance was similar to Alzheimer's disease patients were those more likely to subsequently develop the disease. The Paired Associates Learning task used in these studies assesses memory for the association of patterns with locations. Processing locations has been repeatedly found to be impaired in Alzheimer's disease (Nguyen *et al.*, 2003; Brandt *et al.*, 2005; Kalov *et al.*, 2005; Rosenbaum *et al.*, 2005). However, there is evidence suggesting that location is not the only feature that patients with Alzheimer's disease fail in associating. Lindeboom *et al.* (2002) designed the 'Visual Association Test', a cued recall task in which participants had to remember two interactive pictures (e.g. a monkey holding an umbrella). The authors reported that the Visual Association Test successfully discriminated Alzheimer's disease from vascular dementia, frontotemporal dementia, subcortical dementia and patients with Lewy body dementia with high specificity.

Alzheimer's disease patients have also been shown to be impaired when they had to recall the colours of previously studied figures (Della Sala *et al.*, 2000), or when they had to keep track of conversations with an increasing number of speakers (Alberoni *et al.*, 1992). This deficit in holding associative information in memory in Alzheimer's disease appears to extend to different retrieval processes as well as to a variety of item combinations, as Alzheimer's disease patients have also been found to be impaired in tasks assessing the recognition of pairs of faces with names (Hodges and Greene, 1998), object parts (Tippett *et al.*, 2003) or pairs of words (Gallo *et al.*, 2004). Lloyd-Jones (2005) also used a recognition paradigm in which common objects were associated with congruent (e.g. yellow banana) or incongruent (e.g. purple banana) colours. Although Alzheimer's disease patients demonstrated an intact priming effect, they showed a deficit in explicit memory for colour-object bindings. Lloyd-Jones (2005) suggested that the semantic processes that provide the 'glue' that integrates perceptual features into single units are impaired in Alzheimer's disease. Overall, these studies suggest that some memory deficits shown by Alzheimer's disease patients may represent the breakdown of mechanisms responsible for representing the combination of different features in long-term memory.

However, the studies summarized above cannot determine whether Alzheimer's disease patients show a deficit which is specific to binding information in memory, as none have assessed the extent to which the memory impairment could be accounted for by a deficit in memory for the individual items which compose these complex events. For example, it is unclear how much of the poor performance on the Paired Associates Learning Test of the CANTAB reflects a deficit in recalling locations alone. To offer a precise account of the associative memory problems in Alzheimer's disease from a binding perspective it is essential to assess the extent to which the memory impairment for complex figures is greater than any memory impairment for the independent features composing these figures.

Moreover, the tasks described above were devised to investigate the process of learning associations between items, that is, long-term memory. However, the relation between the mechanisms responsible for learning associations between items in long-term memory and those involved in binding information

in short-term memory into temporary integrated representations is poorly understood. Recent evidence suggests that learning repeated arbitrary bindings of shapes with colours does not impact on short-term memory performance, suggesting that these mechanisms may operate separately in long-term memory (LTM) and short-term memory (STM) (Colzato *et al.*, 2006; Treisman, 2006; Logie *et al.*, 2009). In contrast, Hollingworth (2006, 2007) and Hollingworth *et al.* (2005) found that when people look for changes in natural scenes, what was previously learnt about the associations between stimuli (i.e. LTM) impacts on decisions based on information retained over short periods of times (i.e. STM). This suggests that when complex events encompass meaningful stimulus arrays, there may be a relation between binding processes in STM and LTM. Whether association or 'binding' reflects the function of common mechanisms operating in STM and LTM, whether these mechanisms share resources, or whether they are processes acting independently in LTM and STM are issues yet to be investigated.

In the animal literature (Brown and Warburton, 2006), computational models (Cer and O'Reilly, 2006; Murre *et al.*, 2006), neuroimaging studies (Luo and Niki, 2005) or in the neuropsychology literature (Mayes *et al.*, 2004, 2007), it is posited that associative learning, or 'relational association' (Mayes *et al.*, 2007), is a slow mechanism which is dependent on functional integration in the medial temporal lobe structures, particularly the hippocampus, and cortical regions. Binding, however, also referred to as 'conjunctive association' (Mayes *et al.*, 2007), is considered a faster mechanism which may depend on the interactions between neocortical regions (e.g. frontal regions and posterior parietal structures), and which seems to be more related to STM (Prabhakaran *et al.*, 2000; Todd and Marois, 2004, 2005). In the light of this evidence, it may be argued that LTM deficits for bound information observed in patients with Alzheimer's disease would not necessarily predict STM deficits for bound information in these patients, as these memory systems may be dependent on relatively independent binding mechanisms. However, to date, STM binding has not been investigated in Alzheimer's disease (see Lowndes and Savage, 2007 for an up-to-date review on early detection of Alzheimer's disease and the usefulness of associative memory tasks).

We carried out two experiments aimed at investigating whether the process of binding stimulus features in STM is affected in patients with Alzheimer's disease. To this end, we devised a verbal task to determine whether Alzheimer's disease patients have problems in holding bound features as integrated representations in verbal STM and to determine whether memory for items bound into complex events is impaired in Alzheimer's disease to a greater extent than memory for the individual features composing these complex items.

Experiment 1

Aims

Experiment 1 investigated whether patients in the mild to moderate stages of Alzheimer's disease were able to hold bound information in verbal STM. It also investigated whether any deficit revealed in holding bound items in STM would reflect an impairment over and above memory problems for individual items.

Methods

Participants

The demographic characteristics of the participants recruited into Experiment 1 are shown in Table 1. The two groups did not significantly differ in age and years of education. Patients with Alzheimer's disease were diagnosed according to the diagnostic criteria established by the DSM-IV-TR and the

NINCDS-ADRDA group (McKhann *et al.*, 1984). In addition, Alzheimer's disease patients and healthy elderly were excluded from the study if they showed colour vision problems as assessed by the Dvorine (1963) test of Colour Blindness. All participants gave their signed consent to take part in this study. The neuropsychological profile of patients entering this experiment is shown in Table 2.

Stimuli and apparatus

Participants were assessed using a personal computer running an E-prime script (Psychological Software Tools, Pittsburgh, PA) generated for the study. The program presented participants with arrays of items on the personal computer screen. Healthy elderly were presented with arrays of six items in conditions assessing memory for single features and three items in the condition assessing the binding of these features in memory. Alzheimer's disease patients were presented with arrays of four items in conditions assessing memory for single features and of two items in the condition assessing the binding of these features in memory. These array sizes were chosen based on previous pilot studies which suggested that at this memory load the performance of both healthy elderly and Alzheimer's disease patients on the single feature conditions would be comparable and well away from ceiling and floor levels.

Furthermore, by using these array sizes, memory load, as defined by the number of features, was balanced across conditions (e.g. two items in the binding condition and four items in the single features conditions all presented four features). This allowed the investigation of memory for single features and the binding of these features in a situation where memory load was further controlled.

Items used in these arrays were nameable colours and objects presented individually or as integrated objects. Two sets, one with 11 nameable colours (red, blue, green, brown, orange, yellow, purple, grey, turquoise, pink and black) and another one with 11 nameable objects (bed, apple, banana, bell, shoe, car, book, chair, cup, guitar and button) were used to construct the stimulus arrays. Objects with name frequencies above 100 were taken from the International Picture Naming Project (<http://crl.ucsd.edu/~aszekely/ipnp/>). Colour nameability was piloted in 12 healthy young volunteers with age ranging from 20 to 29 years. Red, blue, green, yellow, purple, grey and black were named using these exact names by 100% of participants, brown by 83%, orange 83%, turquoise 66% (here turquoise, cyan or light blue were valid names whereas blue was considered an error) and pink 83%.

Design

Trial Design: stimuli were presented together in the study array for a total time of 1.5 s per feature. As this task assessed the recall of verbal information, the presentation time used was sufficient to allow the verbal encoding of the studied material by both Alzheimer's disease patients and healthy elderly. By presenting the study array for 1.5 s per feature, the total presentation time was equated across conditions according to the total number of features to be remembered (i.e. colours or objects). Immediately after the study array disappeared, a new screen asked participants to recall verbally (i.e. by naming them aloud) the items they had just seen in no particular order. The experimenter recorded their responses using a scoring sheet.

Procedure

At the beginning of the experiment participants were presented with two separate arrays one consisting of 22 colours and the other consisting of 22 objects. These arrays consisted of the colours and objects used in the experiment and 11 other colours and 11 other objects intermixed within the arrays. Participants were requested to name the colours and the objects to ensure that they had no problems in naming the objects used in the experiment. Only those participants who correctly named all of the objects and colours selected for the experiment were included further. Participants then undertook the four

experimental conditions which were blocked and administered in a counterbalanced order. Each experimental condition consisted of six trials that were fully randomized across participants.

Memory for colours: in this condition the study array consisted of different coloured squares. Participants were given the following instructions: 'Now we will test your memory for colours. You will see six (or four) colours on the screen. You should try to remember as many colours as you can. After these colours disappear, you will have to say aloud all the colours that you have just seen'. *Memory for objects:* in this condition the study array consisted of common objects. Objects were outlines of figures. Participants were given the same instructions outlined above only replacing the term colours with the term objects. *Memory for objects and colours unbound:* in this condition the study array consisted of colours and objects presented as separate entities. Half of the items were coloured squares and the other half were figure outlines of common objects. Participants were instructed as above, but they were told to remember as many objects and as many colours as possible. *Memory for object-colour bindings:* in this condition the study array consisted of different objects filled with different colours. These coloured objects were constructed by randomly combining objects with colours from the two sets. During this condition participants were asked to try to remember 'as many coloured objects as possible, that is remember each object together with the colour in which it was presented'.

Colours and objects were evenly distributed across the different experimental conditions. Individual or bound features could be repeated within conditions but not within a trial. Additionally, identical arrays were never repeated within any experimental condition.

Results

Performance was analysed with a 2 (Group = healthy elderly versus Alzheimer's disease patients) by 4 (Condition = objects only versus colours only versus objects and colours unbound versus object-colour bindings) mixed-ANOVA. Mean performance levels across groups and conditions are shown in the Fig. 1. As expected, Alzheimer's disease patients had poorer overall memory performance than healthy elderly with a significant main effect of Group [$F(1,44) = 50.38, P < 0.001$]. In addition there was also a significant effect of Condition [$F(3,132) = 10.47, P < 0.001$] and a significant interaction between Condition and Group [$F(3,132) = 5.47, P < 0.01$].

Pairwise comparisons were carried out between groups for each of the four experimental conditions separately (four contrasts), and across conditions for each group separately ($4 \times 2 = 8$ contrasts). Hence, with a total of 12 pairwise comparisons the alpha threshold was set at 0.004. Comparisons with P -values below this threshold were assumed to reflect significant differences.

These pairwise comparisons showed that Alzheimer's disease patients performed more poorly than healthy elderly in conditions assessing memory for objects only [mean difference (MD) = 18.36, $P = 0.001$], objects and colours unbound (MD = 19.20, $P < 0.001$), and object-colour binding (MD = 37.20, $P < 0.001$). Alzheimer's disease patients and healthy elderly did not differ significantly in the condition assessing memory for colours only (MD = 14.37, $P = 0.005$).

Further pairwise comparisons across conditions showed that Alzheimer's disease patients' performance in the object-colour binding condition was significantly poorer than in conditions assessing memory for objects only (MD = 24.64, $P < 0.001$), colours only (MD = 22.10, $P < 0.001$) and objects and colours unbound (MD = 23.55, $p < 0.001$). None of the other contrasts for the Alzheimer's disease patients across conditions assessing memory for single or unbound features and none of the contrasts for the healthy elderly resulted in significant differences.

Analysis of errors

As the Alzheimer's disease patient group performed significantly worse in memory for object–colour binding than in the other conditions, an analysis of errors was carried out to assess whether Alzheimer's disease patients were less able to retrieve colours or objects. This analysis was possible because in the condition assessing memory for objects and colours unbound the experimenter scored memory for the whole array and for objects and colours separately. In the condition assessing memory for object–colour binding, the experimenter scored the recall of objects, colours, and of the combination. Therefore, the percentage of objects and colours recalled as single entities in the two conditions was entered in this analysis. Within group, dependent sample *t*-tests were carried out to assess if memory for each feature in the condition assessing object–colour binding differed from memory for each feature in the condition assessing memory for objects and colours unbound (Fig. 2). No differences were found in the healthy elderly group when memory for objects and colours were compared across conditions (objects: MD = 5.79, $t = -1.49$, $P = \text{n.s.}$; colours: MD = 4.34, $t = -1.57$, $P = \text{n.s.}$). Alzheimer's disease patients recalled more objects in the object–colour binding condition than in the unbound condition (MD = 16.66.9, $t = -2.45$, $P < 0.05$). Alzheimer's disease patients were less able to retrieve colours in the condition assessing memory for object–colour binding than in the condition assessing memory for unbound features (MD = 14.49, $t = 2.64$, $P < 0.05$).

It is possible that the poor performance of the Alzheimer's disease patients in the binding condition might simply be due to an impairment in perception of complex stimuli with attention being directed to the objects at the expense of the colour, rather than a specific problem in binding object and colour. If this were the case then the Alzheimer's disease patients should show a very much larger deficit in the binding condition with a larger set size. During Experiment 1 we collected additional data for the Alzheimer's disease patients with larger array sizes (six items for single features and three for bound features). These data were used to determine the optimal array sizes that would allow comparability between the Alzheimer's disease performance and the healthy elderly performance on memory for the single features. Therefore, they were not included in the main analysis between groups. However, we were able to compare performance of Alzheimer's disease patients with two different sets of arrays sizes (6/3 versus 4/2) and to determine whether the perceptual complexity of the visual arrays could have had an impact on patients' binding functions. From a two-way repeated-measures ANOVA, main effects were found for set size [$F(1,22) = 28.39$, $P < 0.001$], whereby larger set sizes resulted in poorer memory performance than smaller set sizes (6/3 items: $M = 39.31\%$, $SD = 16.23$; 4/2 items: $M = 56.70\%$, $SD = 19.79$), and for condition [$F(3,66) = 26.95$, $P < 0.001$], whereby performance on memory for binding of features was found to be the poorest (single features: $M = 54.03\%$, $SD = 17.14$; bound features: $M = 29.95\%$, $SD = 20.64$). However, the interaction was non-significant [$F(3,66) = 0.35$, $P = \text{n.s.}$]. That is, the impact of the binding condition was the same for the larger and the smaller set size, making it unlikely that the results arose from a problem with perceptual complexity, and more likely that Alzheimer's disease patients have a specific impairment of binding in STM.

Discussion

Experiment 1 revealed that the Alzheimer's disease patient group were impaired in verbal STM for bindings between features. This is the first empirical evidence suggesting that Alzheimer's disease also impairs processes responsible for holding bound information in STM when this information is processed within the verbal domain. Moreover, Alzheimer's disease patients' impairment in recalling objects and colours bound was significantly greater than their difficulty in recalling objects only or objects and colours presented as individual features (i.e. objects and colours unbound).

The analysis of the pattern of errors suggested that in patients with Alzheimer's disease retaining colours within bound items seems to be more vulnerable than retaining objects. This finding fits well with

the results reported by Lloyd-Jones (2005), whereby patients with Alzheimer's disease were found to be less able than the healthy controls to use colour-based information when recognizing coloured objects.

The paramount drop in memory performance for objects bound with colours observed in Alzheimer's disease patients contrasts with a preserved memory for this type of complex information in healthy elderly. Brockmole *et al.* (2008) and Parra *et al.* (2009) investigated the process of binding features in visual STM in healthy younger and older adults. Using abstract shapes and colours (Brockmole *et al.*, 2008) and colours bound or unbound into object shapes (Parra *et al.*, 2009), the authors found that healthy older adults had poorer overall memory performance; however, their ability to hold two bound surface features in visual STM was not affected more by age than was their ability to hold individual features (e.g. shapes or colours unbound). The authors concluded that age seems to spare those processes responsible for binding surface features (i.e. shapes and colours) into integrated objects. The current experiment was not designed to investigate age effects on memory binding; however, the finding that healthy elderly had equivalent memory for bound and unbound features supports Brockmole *et al.*'s (2008) and Parra *et al.*'s (2009) observations. This also suggests that the binding deficit appears to be specific to Alzheimer's disease.

A possible caveat to Experiment 1 is that memory performance of the two groups was significantly different in conditions assessing memory for objects only and objects and colours unbound as well as for bound features. Therefore, the significant interaction observed in Experiment 1 could have been driven by a preserved ability of the healthy elderly group to perform a task that did not demand enough cognitive effort. It is known that cognitive impairments in older people are more likely to be apparent in tasks that demand greater cognitive effort (Kester *et al.*, 2002). In order to claim specificity of these binding deficits in Alzheimer's disease, it is important to demonstrate that under increased cognitive demands, as imposed by high memory load, the differences between healthy elderly and Alzheimer's disease patients in the condition assessing memory for bound items persists. This issue was addressed in Experiment 2.

Experiment 2

Aims

Experiment 2 investigated whether the binding deficit observed in Experiment 1 was specific to Alzheimer's disease patients or could be accounted for by a general memory impairment. This was investigated by increasing the overall memory load for the healthy elderly group only. Our predictions were that if STM binding deficits are specific to Alzheimer's disease, this manipulation would reduce the overall memory performance in the healthy elderly group, however the difference between healthy elderly and Alzheimer's disease patients in the condition assessing memory for bound features would remain. If these deficits were not specific to Alzheimer's disease but age-related, the difference between the two groups in the binding condition would be reduced when the task demands were increased.

Methods

Participants

The demographic characteristics of participants entering Experiment 2 are shown in Table 1. Groups were matched for age and years of education. Among the healthy elderly, 18 had taken part in Experiment 1 and out of the 21 Alzheimer's disease patients, 19 took part in Experiment 1. The same inclusion and diagnostic criteria used in Experiment 1 applied. All participants gave their signed consent to take part in this study. The general neuropsychological profile of patients entering this experiment is shown in Table 2.

Procedure

The same task, as described in Experiment 1, was used. However in conditions assessing memory for objects only, colours only and objects and colours unbound, healthy elderly were presented with eight items. In the condition assessing memory for object–colour bindings, healthy elderly were presented with four items. The other task parameters remained the same.

Results

Performance was analysed with a 2 (Group = healthy elderly versus Alzheimer's disease patients) by 4 (Condition = objects only versus colours only versus objects and colours unbound versus object–colour binding) mixed-ANOVA. Mean performance levels across groups and conditions are shown in Fig. 3. Main effects were significant for Group [$F(1,39) = 29.61, P < 0.001$] and Condition [$F(3,117) = 18.82, P < 0.001$]. The interaction was also significant [$F(3,117) = 7.35, P < 0.01$].

Pairwise comparisons performed across groups showed that Alzheimer's disease patients performed more poorly than healthy elderly in the condition assessing memory for object–colour bindings ($MD = 37.20, P < 0.001$). None of the other comparisons resulted in significant differences.

Pairwise comparisons performed across conditions showed that Alzheimer's disease patients' performance in the object–colour binding condition was significantly poorer than in conditions assessing memory for objects only ($MD = 28.17, P < 0.001$), colours only ($MD = 27.38, P = 0.001$) and objects and colours unbound ($MD = 30.95, P < 0.001$). None of the other contrasts carried out in the Alzheimer's disease patients across conditions assessing memory for single or unbound features and none of the contrasts with the healthy elderly resulted in significant differences.

The results revealed that when the healthy elderly and the Alzheimer's disease patients group did not significantly differ in their performance in the condition assessing memory for single and unbound features, the Alzheimer's disease patients were still less able to retain in STM the binding between items as compared with the healthy elderly group.

Analysis of errors

Dependent sample *t*-tests were performed to examine if memory for each feature in the condition assessing object–colour binding differed from memory for each feature in the condition assessing memory for objects and colours unbound (Fig. 4). No differences were found in the performance of the healthy elderly group when memory for objects and colours were compared across conditions (objects: $MD = 4.17, t = -1.04, P = \text{n.s.}$; colours: $MD = 0.42, t = -0.11, P = \text{n.s.}$). Alzheimer's disease patients recalled more colours in the condition assessing memory for objects and colours unbound than in the condition assessing memory for objects bound with colours ($MD = 22.22, t = 4.64, P < 0.001$). No other comparison resulted in a significant difference.

Finally, given that the procedures in the two experiments were comparable we selected those participants who took part in both experiments and carried out a three-way mixed-ANOVA with Group (healthy elderly versus Alzheimer's disease patients) as the between-subjects factor and Experiment (Experiment 1 versus Experiment 2) and Condition (objects only versus colours only versus objects and colours unbound versus object–colour binding) as the within-subjects factors. A total of 18 healthy elderly and 19 Alzheimer's disease patients entered this further analysis designed to investigate the extent to which the experimental manipulation introduced in Experiment 2 had a differential impact on the overall pattern of results observed in Experiment 1.

There was a significant main effect for Experiment [$F(1,35) = 19.84, P < 0.001$], for Group [$F(1,35) = 64.61, P < 0.001$], and Condition [$F(3,105) = 14.86, P < 0.001$]. Significant interactions were found in the analysis of Experiment \times Group [$F(1,35) = 19.84, P < 0.001$], suggesting that the healthy

elderly's performance was affected by the experimental manipulation, and in the analysis of Group \times Condition [$F(3,105) = 6.98, P < 0.001$], whereby the impact that the condition assessing memory for bound items versus single or unbound items had on performance in Alzheimer's disease patients was present across experiments. The other interactions, including the three-way interaction, were not significant, suggesting that the experimental manipulation did not differentially affect the performance pattern across conditions. That is, the Alzheimer's disease group showed a drop in binding performance compared with the other conditions, while the healthy elderly group did not, and this differential effect for the Alzheimer's disease group was present in both experiments.

Discussion

Increasing the task demands in terms of memory load resulted in a drop in memory performance in the healthy elderly group to the extent that the difference between this group and the Alzheimer's disease group observed in Experiment 1 in conditions assessing memory single or unbound features were removed. This notwithstanding, the main outcome of Experiment 1 was replicated (i.e. Alzheimer's disease patients showed a paramount impairment in binding information in verbal STM). The analysis of errors also confirmed the findings from Experiment 1. Patients with Alzheimer's disease were less able to retrieve colour-based compared to object-based information. Therefore, in two separate experiments we provided additional support for the findings by Lloyd-Jones (2005), who suggested that Alzheimer's disease patients cannot use colour-based information when remembering coloured objects. This finding is now extended to binding in verbal STM.

The finding that memory for single or unbound features and memory for bound features is not significantly different in the healthy elderly group in both experiments suggests that memory for bound features is equivalent to memory for the same type and amount of individual features that are presented separately. This finding is consistent with results reported by Brockmole *et al.* (2008) and Parra *et al.* (2009) who reported that adults can remember shapes bound with colours or shapes alone equally well. This also supports the suggestion that age *per se* does not affect those processes responsible for integrating features in STM (Brockmole *et al.*, 2008; Parra *et al.*, 2009). Finally, the three-way ANOVA suggested that the experimental manipulation had an overall effect on performance in healthy elderly, that is it decreased differences between groups in conditions assessing memory for single or unbound features, but this manipulation did not modify the pattern of results observed in Experiment 1, i.e. the selective binding deficit in the Alzheimer's disease group.

General discussion

The results of the experiments presented here support the hypothesis that the deficit in binding information in verbal STM in patients with Alzheimer's disease is more pronounced than their memory impairment for unrelated information. In both experiments, patients with Alzheimer's disease performed significantly more poorly when they had to retrieve bound information than when they had to remember individual or unbound features. Swainson *et al.* (2001) reported that patients with Alzheimer's disease performed worse than healthy older adults when they had to recall associations of patterns with locations during a learning paradigm. Although not acknowledged by the authors, this suggests that binding information may be impaired in Alzheimer's disease. However, they did not assess whether this deficit was due to a difficulty in holding in memory the association of patterns with locations or just to a difficulty in holding locations in memory. In the current experiments we disentangled memory for bindings from memory for features and moreover have demonstrated a deficit in temporary binding in verbal STM in these patients.

There are two methodological characteristics of our study that make the finding of impaired memory for bound information in Alzheimer's disease relevant. In the current study we controlled

memory load across conditions by keeping constant the number of features. Additionally, the memory load for Alzheimer's disease patients was kept within their capacity by presenting two objects in the condition assessing memory for bound information as compared to three or four objects presented to healthy elderly in Experiments 1 and 2, respectively. This allowed us to equate overall memory performance between the Alzheimer's disease and healthy elderly groups for the single feature and unbound memory conditions. Using this experimental manipulation, patients with Alzheimer's disease presented with a paramount memory deficit for bound information, in particular, in recalling colour-based information within bound colour-object items. By equating performance for conditions assessing memory for single and unbound features, this memory binding difficulty cannot be attributed to an overall memory impairment.

Moreover, the additional analysis carried out in the Alzheimer's disease group, using two different sets of array sizes, revealed that the impairment in the ability to hold bound features in STM is unlikely to have arisen from problems in dealing with perceptual complexity.

It might be argued that the task presented here could have tapped LTM as visual arrays were composed of highly nameable features (with strong semantic representations) and were presented for relatively long periods of times (e.g. 9 s when six features were shown). However, when constructing arrays of coloured objects, colours and objects were randomly combined, with colours and objects repeated across trials in different combinations. This made it unlikely that pairing features would be semantically based. Secondly, objects and colours were evenly repeated across conditions; but there was no repetition of individual or bound features within trials nor was there repetition of particular combinations of features or objects in specific locations. Memory traces for a given trial would therefore be overwritten by the array presented in the following trial, making it less likely that any long term representation of these arbitrary and rapidly changing associations could be formed (for a discussion on learning and binding during STM tasks see also Colzato *et al.*, 2006, Logie *et al.*, 2009 and Treisman, 2006). Given that we specifically avoided semantic associations between objects and colours, our task was not devised to address the issue on whether Alzheimer's disease patients had an inability to over-ride typical semantic associations (e.g. yellow-banana). However, the results from previous studies also assessing memory for object-colour combination (Della Sala *et al.*, 2000; Lloyd-Jones, 2005) suggest that it does not seem to be the content of these bindings or the availability of semantic clues that determines the breakdown of memory binding processes in Alzheimer's disease. Therefore, we suggest that the difficulties observed in patients with Alzheimer's disease represent a genuine deficit in holding in verbal STM associations or 'bindings' of different types of features in unified representations.

This is the first empirical evidence reporting that Alzheimer's disease affects the process of binding information in STM. We can also conclude that the procedures used in these experiments allowed us to separate the contribution of memory for individual items and for bound items in recalling complex events. Therefore, the results provide reliable evidence of the contribution of memory for unrelated or related information to the overall memory impairment observed in patients with Alzheimer's disease.

As STM binding is not affected by normal ageing (Brockmole *et al.*, 2008; Parra *et al.*, 2009), these findings could prove clinically relevant. It is important to develop clinical tools which specifically assess cognitive impairment due to Alzheimer's disease independently of any contribution due to age (c.f., MacPherson *et al.*, 2007).

The present findings have demonstrated a deficit in binding in Alzheimer's disease for information which can easily be verbalized. Future research should investigate the extent to which the breakdown of the mechanisms responsible for unitizing features in STM via verbal codes also account for the associative learning problems observed in Alzheimer's disease for other forms of associations (e.g. objects and locations). The associative learning tasks reported in the literature on Alzheimer's disease have not separated memory for bindings from memory for features. Furthermore, we reported here that binding in verbal STM is affected by Alzheimer's disease however, as verbal and visual STM are functions subserved by different mechanisms, it would also be worth investigating whether those processes

responsible for unitizing visual features in STM are impaired by Alzheimer's disease. This would determine whether the binding deficit found in the experiments reported here can be considered a universal feature of Alzheimer's disease affecting all memory systems and retrieval processes.

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Footnotes

Abbreviations:

CANTAB: Cambridge Neuropsychological Test Automated Battery

LTM: long-term memory

STM: short-term memory

References

- Alberoni M, Baddeley A, Della Sala S, Logie R, Spinnler H. Keeping track of a conversation: impairments in Alzheimer's disease. *Int J Geriatr Psychiatry* 1992; 7: 639–46.
- Blackwell AD, Sahakian BJ, Vesey R, Semple JM, Robbins TW, Hodges JR. Detecting dementia: novel neuropsychological markers of preclinical Alzheimer's disease. *Dement Geriatr Cogn Disord* 2004; 17:42–8.
- Brandt J, Shpritz B, Munro CA, Marsh L, Rosenblatt A. Differential impairment of spatial location memory in Huntington's disease. *J Neurol Neurosurg Psychiatry* 2005; 76: 1516–9.
- Brockmole JR, Parra MA, Della Sala S, Logie R. Do binding deficits account for age-related decline in visual working memory? *Psychon Bull Rev* 2008; 15: 543–7.
- Brown MW, Warburton EC. Association and dissociation in recognition memory systems. In: Zimmer HD, Mecklinger A, Lindenberger U, editors. *Handbook of Binding and Memory, Perspective from Cognitive Neuroscience*. New York: Oxford University Press; 2006. pp. 413–43.
- Cer DM, O'Reilly RC. Neural Mechanisms of binding in the hippocampus and neocortex: insights from computational models. In: Zimmer HD, Mecklinger A, Lindenberger U, editors. *Handbook of binding and memory, perspective from cognitive neuroscience*. New York: Oxford University Press; 2006. pp. 193–220.
- Colzato LS, Raffone A, Hommel B. What do we learn from binding features? Evidence for multilevel feature integration. *J Exp Psychol Hum Percept Perform* 2006; 32: 705–16.
- Della Sala S, Kinnear P, Spinnler H, Stangalino C. Color-to-figure matching in Alzheimer's disease. *Arch Clin Neuropsychol* 2000; 15: 571–85.
- Dvorine I. Quantitative classification of color blind. *J Gen Psychol* 1963; 68: 255–65.

- Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12: 189–98.
- Fowler KS, Saling MM, Conway EL, Semple JM, Louis WJ. Paired associate performance in the early detection of DAT. *J Int Neuropsychol Soc* 2002; 8: 58–71.
- Gallo DA, Sullivan AL, Daffner KR, Schacter DL, Budson AE. Associative recognition in Alzheimer's disease: evidence for impaired recall-to-reject. *Neuropsychology* 2004; 18: 556–63.
- Giovagnoli AR, Del PM, Mascheroni S, Simoncelli M, Laiacina M, Capitani E. Trail making test: normative values from 287 normal adult controls. *Ital J Neurol Sci* 1996; 17: 305–9.
- Hodges JR, Greene JD. Knowing about people and naming them: can Alzheimer's disease patients do one without the other? *Q J Exp Psychol A* 1998; 51: 121–34.
- Hollingworth A. Scene and position specificity in visual memory for objects. *J Exp Psychol Learn Mem Cogn* 2006; 32: 58–69.
- Hollingworth A. Object-position binding in visual memory for natural scenes and object arrays. *J Exp Psychol Hum Percept Perform* 2007; 33: 31–47.
- Hollingworth A, Hyun JS, Zhang W. The role of visual short-term memory in empty cell localization. *Percept Psychophys* 2005; 67: 1332–43.
- Kalov E, Vlcek K, Jaroly'nov E, Bures J. Allothetic orientation and sequential ordering of places is impaired in early stages of Alzheimer's disease: corresponding results in real space tests and computer tests. *Behav Brain Res* 2005; 159: 175–86.
- Kester JD, Benjamin AS, Castel AD, Craik FIM. Memory in elderly people. In: Baddeley A, Wilson B, Kopelman M, editors. *Handbook of memory disorders*. 2nd edn. London: Wiley; 2002. pp. 543–68.
- Lindeboom J, Schmand B, Tulner L, Walstra G, Jonker C. Visual association test to detect early dementia of the Alzheimer type. *J Neurol Neurosurg Psychiatry* 2002; 73: 126–33.
- Lloyd-Jones TJ. The role of color in the implicit memory performance of healthy older adults and individuals with Alzheimer's disease. *Neuropsychology* 2005; 19: 44–53.
- Logie R, Brockmole JR, Vandenbroucke ARE. Bound feature combinations in visual short term memory are fragile but influence long-term learning. *Vis Cogn* 2009; 17: 160–79.
- Lowndes G, Savage G. Early detection of memory impairment in Alzheimer's disease: a neurocognitive perspective on assessment. *Neuropsychol Rev* 2007; 17: 193–202.
- Luo J, Niki K. Does hippocampus associate discontinuous events? Evidence from event-related fMRI. *Hippocampus* 2005; 15: 141–8.
- MacPherson SE, Della Sala S, Logie RH, Wilcock GK. Specific AD impairment in concurrent performance of two memory tasks. *Cortex* 2007; 43: 858–65.
- Mayes A, Montaldi D, Migo E. Associative memory and the medial temporal lobes. *Trends Cogn Sci* 2007; 11: 126–35.
- Mayes AR, Holdstock JS, Isaac CL, Montaldi D, Grigor J, Gummer A, et al. Associative recognition in a patient with selective hippocampal lesions and relatively normal item recognition. *Hippocampus* 2004; 14: 763–84.
- McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDSADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984; 34: 939–44.
- Murre JM, Wolters G, Raffone A. Binding in working memory and longterm memory: towards an integrated model. In: Zimmer HD, Mecklinger A, Lindenberger U, editors. *Handbook of binding and memory, perspective from cognitive neuroscience*. New York: Oxford University Press; 2006. pp. 221–50.
- Nguyen AS, Chubb C, Huff FJ. Visual identification and spatial location in Alzheimer's disease. *Brain Cogn* 2003; 52: 155–66.

- O'Connell H, Coen R, Kidd N, Warsi M, Chin AV, Lawlor BA. Early detection of Alzheimer's disease (AD) using the CANTAB paired Associates Learning Test. *Int J Geriatr Psychiatry* 2004; 19: 1207–8.
- Orsini A, Grossi D, Capitani E, Laiacona M, Papagno C, Vallar G. Verbal and spatial immediate memory span: normative data from 1355 adults and 1112 children. *Ital J Neurol Sci* 1987; 8: 539–48.
- Parra MA, Abrahams S, Logie R, Della Sala S. Age and binding withindimension features in visual short term memory. *Neurosci Lett* 2009;449: 1–5.
- Prabhakaran V, Narayanan K, Zhao Z, Gabrieli JD. Integration of diverse information in working memory within the frontal lobe. *Nat Neurosci* 2000; 3: 85–90.
- Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. *Am J Psychiatry* 1982; 139: 1136–9.
- Rosenbaum RS, Gao F, Richards B, Black SE, Moscovitch M. “Where to?” remote memory for spatial relations and landmark identity in former taxi drivers with Alzheimer's disease and encephalitis. *J Cogn Neurosci* 2005; 17: 446–62.
- Spinnler H, Tognoni G. Standardizzazione e taratura italiana di test neuropsicologici. *Ital J Neurol Sci* 1987; 6 (Suppl. 8): 9–120.
- Swainson R, Hodges JR, Galton CJ, Semple J, Michael A, Dunn BD, et al. Early detection and differential diagnosis of Alzheimer's disease and depression with neuropsychological tasks. *Dement Geriatr Cogn Disord* 2001; 12: 265–80.
- Memory binding in Alzheimer's disease *Brain* 2009; 132: 1057–1066 | 1065
Downloaded from <http://brain.oxfordjournals.org/> at Edinburgh University on September 4, 2013
- Tippett LJ, Blackwood K, Farah MJ. Visual object and face processing in mild-to-moderate Alzheimer's disease: from segmentation to imagination. *Neuropsychologia* 2003; 41: 453–68.
- Todd JJ, Marois R. Capacity limit of visual short-term memory in human posterior parietal cortex. *Nature* 2004; 428: 751–4.
- Todd JJ, Marois R. Posterior parietal cortex activity predicts individual differences in visual short-term memory capacity. *Cogn Affect Behav Neurosci* 2005; 5: 144–55.
- Treisman A. Objects tooken, binding, and visual memory. In: Zimmer HD, Mecklinger A, Lindenberger U, editors. *Handbook of binding and memory, perspective from cognitive neuroscience*. New York: Oxford University Press; 2006. pp. 315–38.
- Treisman AM, Gelade G. A feature-integration theory of attention. *Cognit Psychol* 1980; 12: 97–136.
- Tulving E. Episodic memory: from mind to brain. *Annu Rev Psychol* 2002; 53: 1–25.
- Warrington E, James M. Visual object and space perception battery (VOSP). UK: Thames Valley Test Company; 1991.
- Zimmer HD, Mecklinger A, Lindenberger U. Levels of binding: types, mechanisms, and functions of binding. In: Zimmer HD, Mecklinger A, Lindenberger U, editors. *Handbook of binding and memory, perspective from cognitive neuroscience*. New York: Oxford University Press; 2006. pp. 3–25.

Tables and Figures

Table 1

Demographic characteristics of participants in Experiments 1 and 2

	Experiment 1			Experiment 2		
	Healthy elderly (<i>n</i> = 23)	Alzheimer's disease patients (<i>n</i> = 23)	<i>t</i> df = 44	Healthy elderly (<i>n</i> = 20)	Alzheimer's disease patients (<i>n</i> = 21)	<i>t</i> df = 39
Age						
Mean (SD)	69.78 (6.47)	73.26 (6.09)	−1.87 ^{NS}	69.35 (6.02)	73.33 (6.71)	−1.97 ^{NS}
Range	60–82	60–80		61–82	60–83	
Education						
Mean (SD)	7.08 (2.81)	6.39 (3.34)	0.76 ^{NS}	7.25 (2.97)	6.81 (3.66)	0.42 ^{NS}
Range	5–13	2–17		5–13	3–17	

(NS = non-significant, $P > 0.05$)

Table 2.

Neuropsychological profile of Alzheimer's disease patients in Experiments 1 and 2

	Experiment 1 (<i>n</i> = 23)			Experiment 2 (<i>n</i> = 21)			
	Cut-off score	Mean \pm SD	Range	No. of patients performing below cut-off	Mean \pm SD	Range	No. of patients performing below cut-off
MMSE	>24	18.70 \pm 3.40	14–24	21	18.60 \pm 3.3	14–24	21
GDS	\geq 5	5.61 \pm 0.50	5–6	23	5.5 \pm 0.5	5–6	21
VOSP—shape detection	<15	19.2 \pm 1.2	16–20	0	19.3 \pm 1.1	16–20	0
Delayed prose recall	4.5 ^a	0.5 \pm 1.4	0–5	21	0.6 \pm 1.3	0–5	19
Digit forward span	2.75 ^b	4.2 \pm 0.8	3–6	0	4.2 \pm 0.8	3–6	0
Raven progressive matrices	14.75 ^a	17.7 \pm 4.6	6–24	5	18.4 \pm 5.1	10–24	6
Trial making test B–A	185 ^c	250.7 \pm 84.6	102–464	17	254.8 \pm 98.4	102–464	15
Category fluency	7.0 ^a	11.0 \pm 6.8	0–25	7	12.4 \pm 8.0	0–25	6

GDS = Global Deterioration Scale (Reisberg *et al.*, 1982); MMSE = Mini Mental State Examination (Folstein *et al.*, 1975); VOSP = Visual Object and Space Perception battery (Warrington and James, 1991).

a Spinnler and Tognoni (1987), b Orsini *et al.* (1987), c Giovagnoli *et al.* (1996), (a, b and c): Cut-off scores equal the inferred 5-centile of the normal population distribution.

Fig. 1. Percentage of correct recall in the Group by Condition analysis of Experiment 1 (error bars represent the standard errors of the mean).

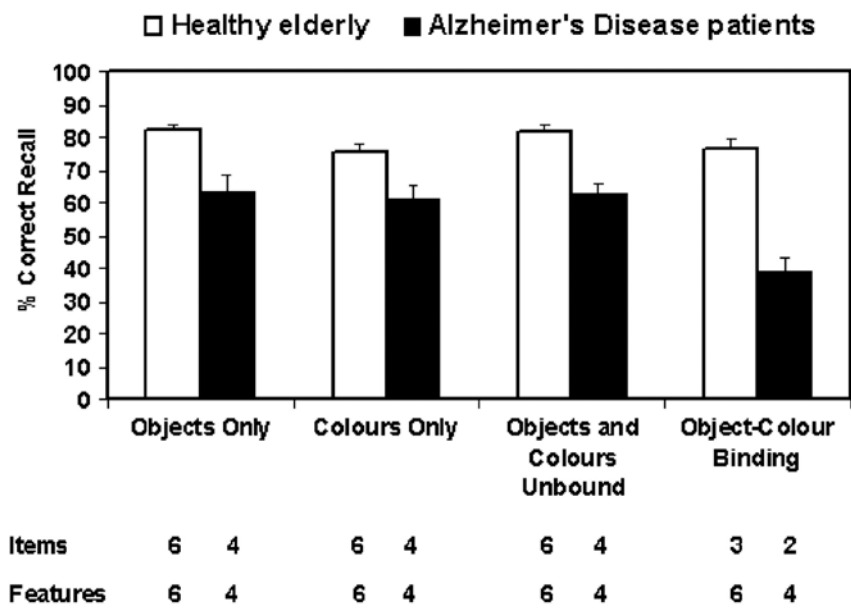


Fig. 2. Percentage of features correctly recalled in conditions assessing memory for objects and colours unbound and object–colour binding of Experiment 1 for healthy elderly and Alzheimer's disease patients (error bars represent the standard errors of the mean).

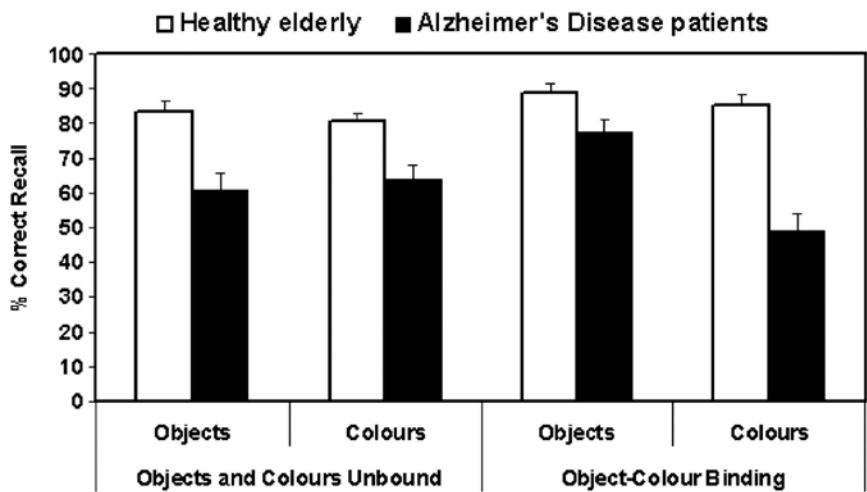


Fig. 3. Percentage of correct recall in the Group by Condition analysis of Experiment 2 (error bars represent the standard errors of the mean).

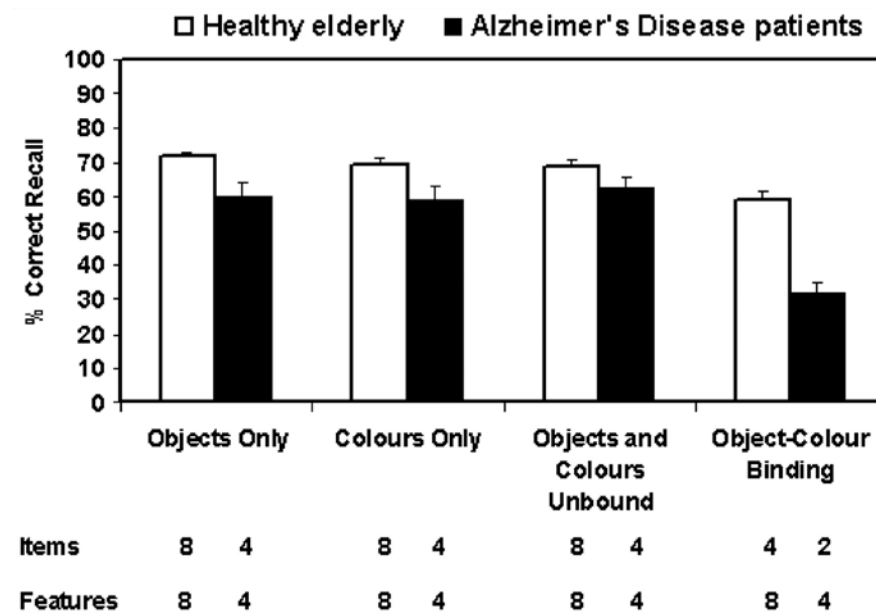


Fig. 4. Percentage of features correctly recalled in conditions assessing memory for objects and colours unbound and object–colour binding in Experiment 2 for healthy elderly and Alzheimer's disease patients (error bars represent the standard errors of the mean)

